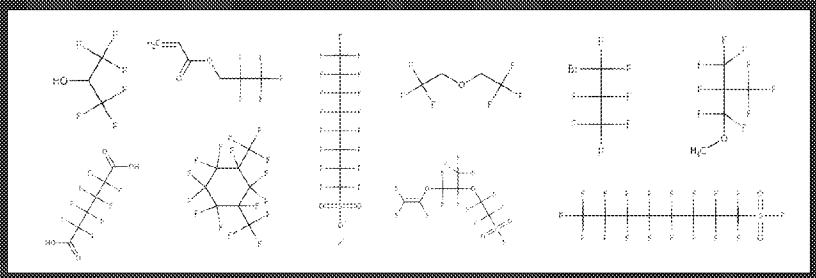
EPA
United States
Environmental Protection
Agency

A Chemical Category-Based Approach for Selecting and Screening PFAS for Toxicity and Toxicokinetic Testing



Briefing for Office of Policy
June 14, 2021

Rusty Thomas
Director
Center for Computational Toxicology & Exposure

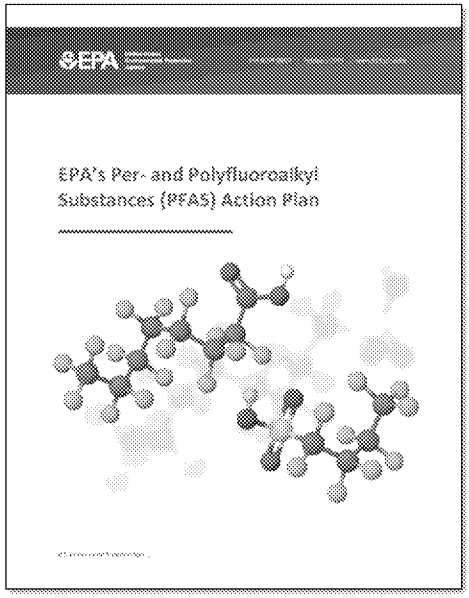
0

Current State of the Science

- There continues to be an evolving definition of what constitutes a PFAS
- There is emerging consensus on the need to use class/grouping-based approaches to assess and potentially regulate PFAS due to the number of PFAS in commerce and the environment.
- There is minimal consensus on what class/grouping-based approach should be taken to assess and potentially regulate PFAS
  - Multiple approaches have been proposed based on various properties (e.g., persistence, mobility, bioaccumulation), exposure, and effects.
- Historically, for human health assessment within EPA, PFAS analogs and/or groups are based on a combination of chain-length and functional group.
  - The number of PFAS analog and/or groups and the associated divisions used in assessments are dependent on the availability of toxicity data (or lack thereof).

EPA
United States
Environmental Protection
Agency

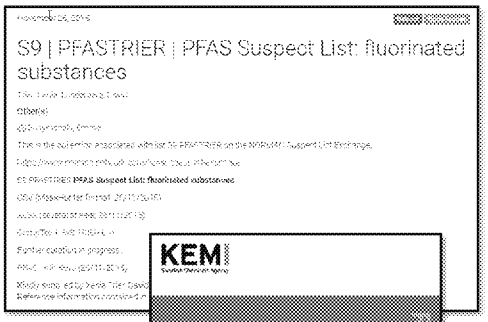
EPA is Using New Approach Methods to Help Fill Information Gaps

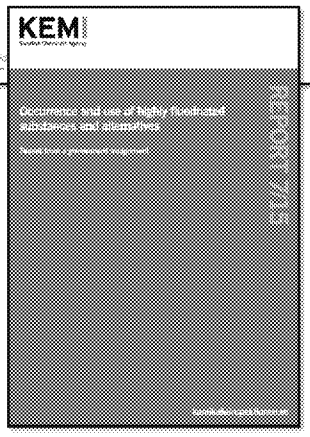


***Research Area 1**: What are the human health and ecological effects of exposure to PFAS?*

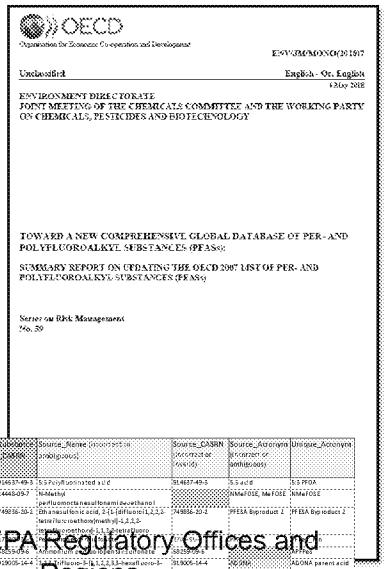
- Using computational toxicology approaches to fill in gaps. For the many PFAS for which published peer-reviewed data are not currently available, the EPA plans to use new approaches such as high throughput and computational approaches to explore different chemical categories of PFAS, to inform hazard effects characterization, and to promote prioritization of chemicals for further testing. These data will be useful for filling gaps in understanding the toxicity of those PFAS with little to no available data. ***In the near term,*** the EPA intends to complete assays for a representative set of 150 PFAS chemicals, load the data into the CompTox Chemicals Dashboard for access, and provide peer-reviewed guidance for stakeholders on the use and application of the information. ***In the long term,*** the EPA will continue research on methods for using these data to support risk assessments using New Approach Methods (NAMs) such as read-across and transcriptomics, and to make inferences about the toxicity of PFAS mixtures which commonly occur in real world exposures. The EPA plans to collaborate with NIEHS and universities to lead the science in this area and work with universities, industry, and other government agencies to develop the technology and chemical standards needed to conduct this research.

It Starts With Chemistry… Curating Names, Structures, and Identifiers


S9 | PFASTRIER | PFAS Suspect List: fluorinated substances


KEM

Occurrence and use of highly fluorinated substances and alternatives


OECD

Organisation for Economic Co-operation and Development

ENV/JM/MONO(2015)7

Unclassified

English - Or. English

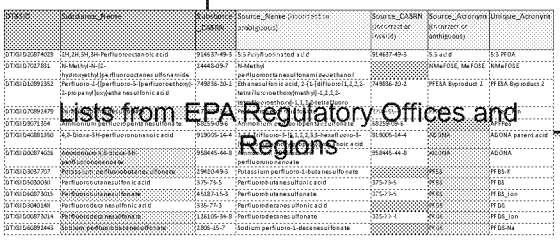
4 May 2015

ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

TOWARD A NEW COMPREHENSIVE GLOBAL DATABASE OF PER- AND POLYFLUOROALKYL SUBSTANCES (PFASs):

SUMMARY REPORT ON UPDATING THE OECD 2007 LIST OF PER- AND POLYFLUOROALKYL SUBSTANCES (PFASs)

Series on Risk Management
No. 39



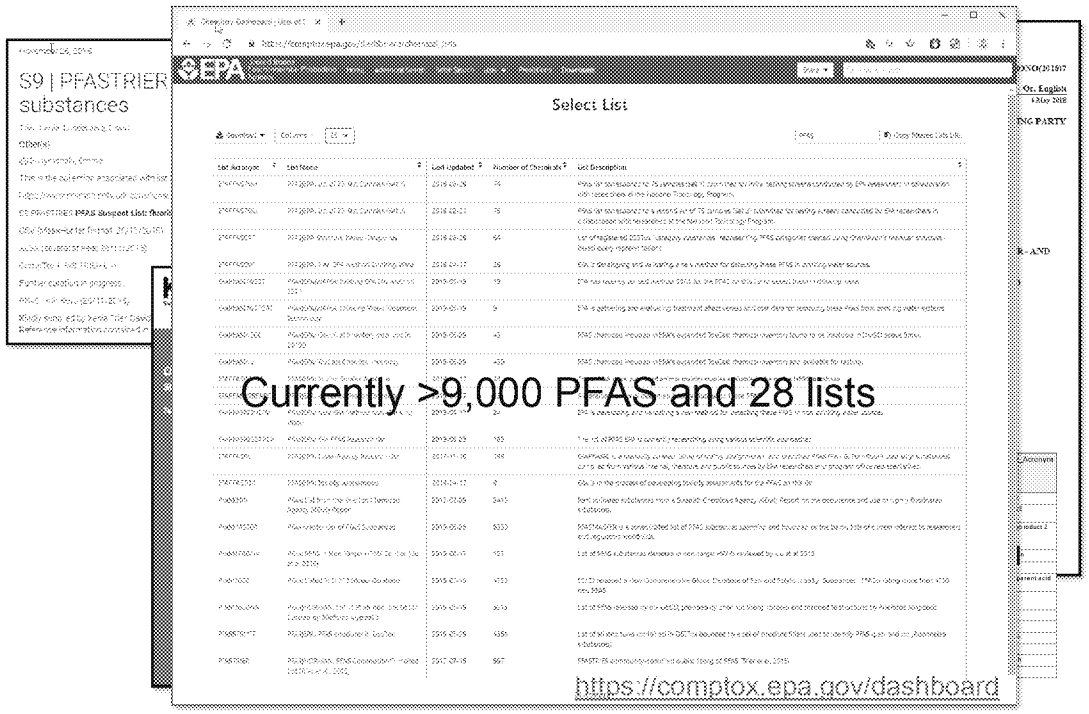
DTXSID	Substance_Name	Substance_CASRN	Source_Name (incorrect or ambiguous)	Source_CASRN (incorrect or invalid)	Source_Acronym (incorrect or ambiguous)	Unique_Acronym
DTXSID20874039	1H,1H,2H,2H-Perfluorooctanoic acid	27854-31-5	5:3 Polyfluorinated acid	914637-49-3	5:3 acid	5:3 PFCA
DTXSID70227861	N-Methyl-N-(2-hydroxyethyl)perfluorooctanesulfonamide	24448-09-7	N-Methyl perfluorooctanesulfonamidoethanol		NMeFOSE, MeFOSE	NMeFOSE
DTXSID10891352	Perfluoro-2-(perfluoro-3-(perfluoroethoxy)-2-propoxy)ethanesulfonic acid	749836-20-2	Ether sulfonic acid, 2-[1-[difluoro(1,2,2,2-tetrafluoroethoxy)methyl]-1,2,2,2-tetrafluoroethoxy]-1,1,2,2-tetrafluoro	749836-20-2	PFESA Byproduct 1	PFESA Byproduct 1
DTXSID70991479	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
DTXSID90971354	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
DTXSID40888350	4,8-Dioxa-3H-perfluorononanoic acid	919005-14-4	4,8-dioxa-3H-perfluorononanoic acid	919005-14-4	ADONA	ADONA parent acid
DTXSID60874026	Ammonium 4,8-dioxa-3H-perfluorononanoate	958445-44-8	Ammonium 4,8-dioxa-3H-perfluorononanoate	958445-44-8	ADONA	ADONA
DTXSID3037707	Potassium perfluoro(4-ethylcyclohexane)sulfonate	1240249-8	Potassium perfluoro(4-ethylcyclohexane)sulfonate		PFECHS	PFECHS
DTXSID5060090	Perfluorooctanesulfonic acid	375-73-5	Perfluorooctanesulfonic acid	375-73-5	PFOS	PFOS
DTXSID40877015	Perfluorooctanesulfonate	45187-15-3	Perfluorooctanesulfonate	375-73-5	PFOS	PFOS_ion
DTXSID30960149	Perfluorodecanesulfonic acid	335-77-3	Perfluorodecanesulfonic acid		PFDS	PFDS
DTXSID60877014	Perfluorodecanesulfonate	119105-94-8	Perfluorodecanesulfonate	335-77-3	PFDS	PFDS_ion
DTXSID60894445	Sodium perfluorooctanesulfonate	2806-15-7	Sodium perfluoro-1-decanesulfonate		PFDS	PFDS-Na

Lists from EPA Regulatory Offices and Regions

Office of Research and Development

Antony Williams, Ann Richard, Chris Grulke, and Chemical Curation Team

It Starts With Chemistry… Curating Names, Structures, and Identifiers



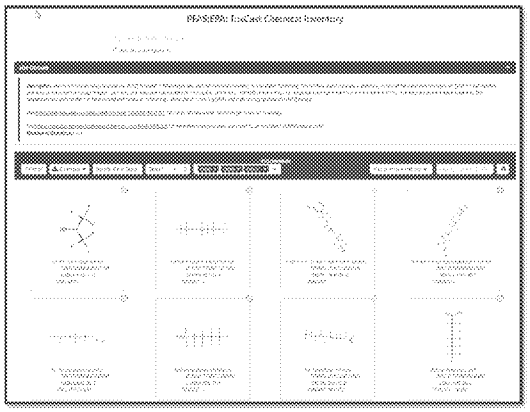
Currently >9,000 PFAS and 28 lists

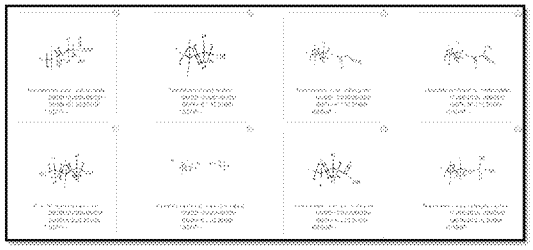
https://comptox.epa.gov/dashboard

Office of Research and Development

Antony Williams, Ann Richard, Chris Grulke, and Chemical Curation Teams

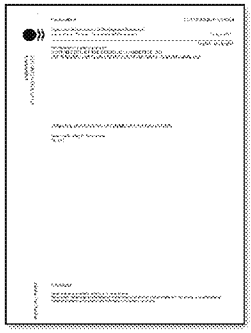
Assembled a PFAS Chemical Library for Research and Methods Development

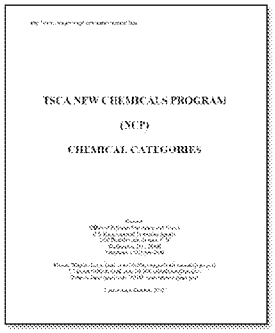


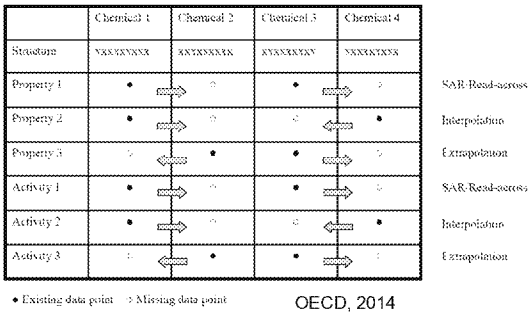


- Attempted to procure ~3,000 based on chemical diversity, Agency priorities, and other considerations
- Obtained 480 total unique chemicals
- Initially selected 150 PFAS in two phases for testing
  - Issues with sample stability and volatility
- Currently, over 100 have passed quality control and are undergoing Tier 1 testing

What are Chemical Category and Read Across Approaches?



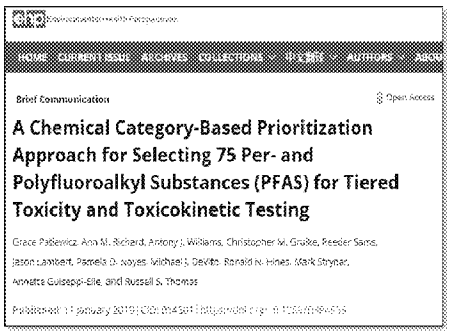




OECD, 2014

- Read-across is a data gap filling technique to infer the property or activity of a chemical using an analogue or category approach
- "Analogue approach" refers to grouping based on a very limited number of chemicals (e.g., target substance + source substance)
- "Category approach" is used when grouping is based on a more extensive range of analogues (e.g., 3 or more members)
- A chemical category is a group of chemicals whose physico-chemical, human heath, environmental toxicological and/or environmental fate properties are likely to be similar or follow a regular pattern as a result of structural similarity (or other similarity characteristics).

Selecting a Subset of PFAS for Tiered Toxicity and Toxicokinetic Testing

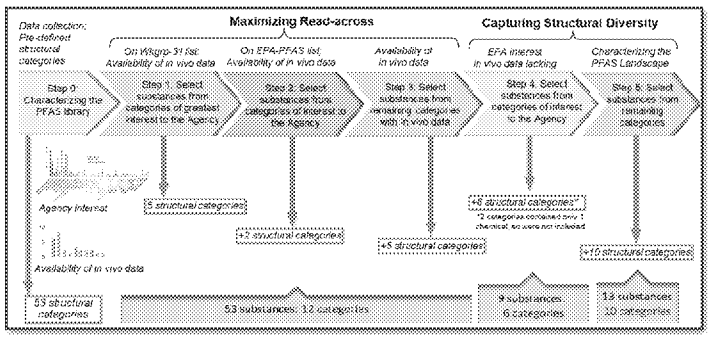


Brief Communication

Open Access

A Chemical Category-Based Prioritization Approach for Selecting 75 Per- and Polyfluoroalkyl Substances (PFAS) for Tiered Toxicity and Toxicokinetic Testing

Grace Patlewicz, Ann M. Richard, Antony J. Williams, Christopher M. Grulke, Reeder Sams, Jason Lambert, Pamela D. Noyes, Michael S. DeVito, Ronald N. Hines, Mark Strynar, Annette Guiseppi-Elie, and Russell S. Thomas



- Selected 150 substances to support development and refinement of categories and read-across evaluation.
- Incorporated substances of interest to Agency.
- Tested substances in a range of assays to characterize mechanistic and toxicokinetic properties.

EPA United States Environmental Protection Agency

In Vitro Toxicity and Toxicokinetic Testing

Toxicological Response	Assay	Assay Endpoints	Purpose
Hepatotoxicity	3D HepaRG assay	Cell death and transcriptomics	Measure cell death and changes in important biological pathways
Developmental Toxicity	Zebrafish embryo assay	Lethality, hatching status and structural defects	Assess potential teratogenicity
Immunotoxicity	Bioseek Diversity Plus	Protein biomarkers across multiple primary cell types	Measure potential disease and immune responses
Developmental Neurotoxicity	Microelectrode array assay (rat primary neurons)	Neuronal electrical activity	Impacts on neuron function
Endocrine Disruption	ACEA real-time cell proliferation assay (T47D)	Cell proliferation	Measure ER activity
General Toxicity	Attagene cis- and trans- Factorial assay (HepG2)	Nuclear receptor and transcription factor activation	Activation of key receptors and transcription factors involved in hepatotoxicity
	High-throughput transcriptomic assay (multiple cell types)	Cellular mRNA	Measures changes in important biological pathways
	High-throughput phenotypic profiling (multiple cell types)	Nuclear, endoplasmic reticulum, nucleoli, golgi, plasma membrane, cytoskeleton, and mitochondria morphology	Changes in cellular organelles and general morphology

Toxicokinetic Parameter	Assay	Assay Endpoints	Purpose
Intrinsic hepatic clearance	Hepatocyte stability assay (primary human hepatocytes)	Time course metabolism of parent chemical	Measure metabolic breakdown by the liver
Plasma protein binding	Ultracentrifugation assay	Fraction of chemical not bound to plasma protein	Measure amount of free chemical in the blood

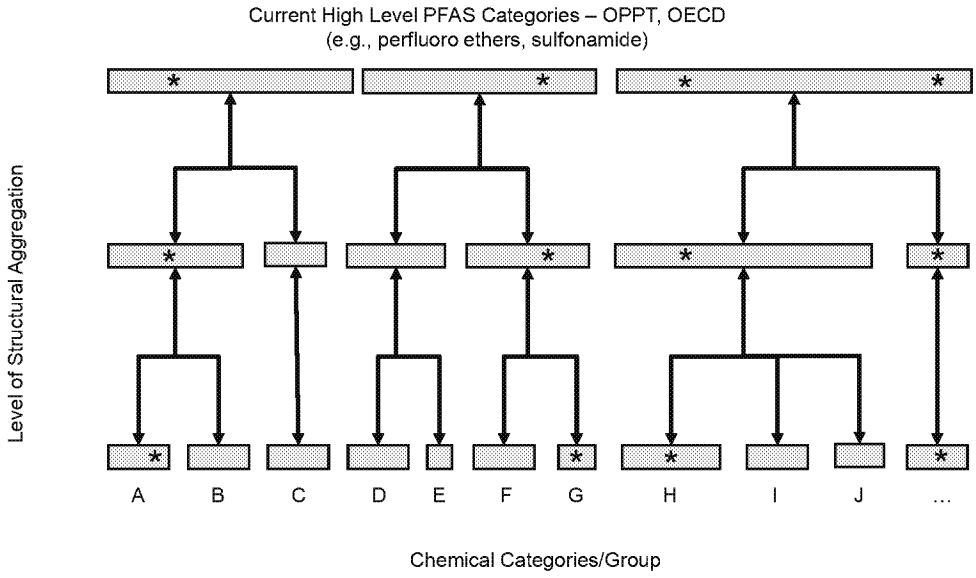
Toxicokinetic Assays being performed by NTP and EPA

EPA United States Environmental Protection Agency

Other Related Activities

- Extracting data from literature and other sources
  - Human hazard (working with CPHEA on evidence mapping)
  - Exposure
  - Physical Chemical Properties
  - Environmental Fate/Bioaccumulation
- Ecological toxicity testing and field studies (more information can be provided if desired)

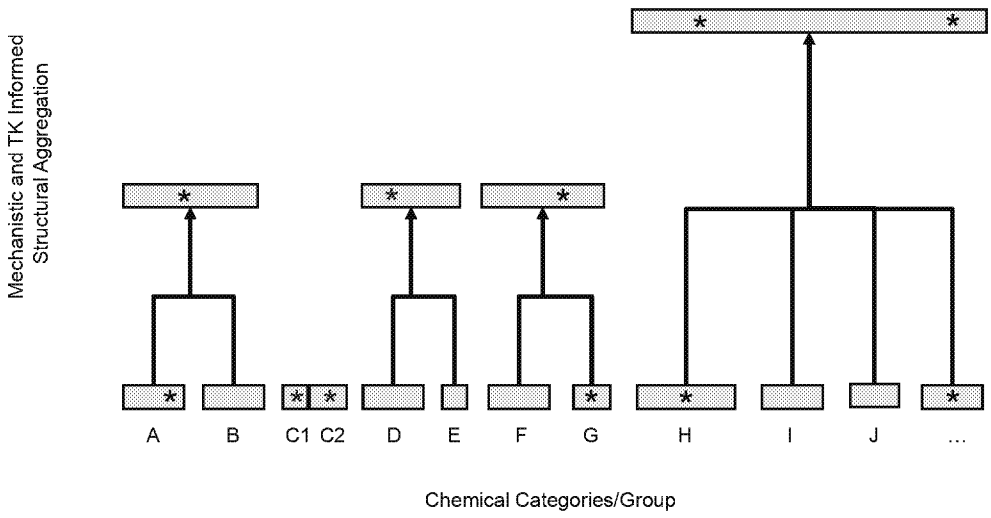
Conceptual PFAS Grouping Approach



Office of Research and Development

*Available source *in vivo* tox study

Conceptual PFAS Grouping Approach



Office of Research and Development

*Needed *in vivo* tox study *Available source *in vivo* tox study

Anticipated Timelines

- Most of the *in vitro* testing to be complete by Summer 2021
  - Some tests may be further delayed due to Covid (e.g., zebrafish embryo assay)
- Draft report by Fall/Winter 2021
- Peer review report by Summer 2022

*Timelines may shift depending on Covid, data availability, etc.